

Spectrum of Pattern Dystrophy in Pseudoxanthoma Elasticum

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Objective: To study the prevalence, type, and features of pattern dystrophy in patients with pseudoxanthoma elasticum (PXE).

Methods: A search of the photographic records at the Vanderbilt Eye Institute using the keywords "angioid streaks and pseudoxanthoma elasticum" yielded 28 names. Of the 23 subjects meeting the patient selection criteria, 22 were confirmed to have a positive diagnosis for PXE after reviewing the medical history information. The diagnosis was confirmed by the constellation of fundus findings in all 22 subjects, by a clinical examination of the skin in 9, and by a skin biopsy specimen in 1.

Results: Pattern dystrophy was present in 16 patients (27 eyes) of those with PXE. Fourteen patients (23 eyes) had fundus pulverulentus, 3 patients (5 eyes) had butterfly-shaped dystrophy, and 1 patient (2 eyes) each had fundus flavimaculatus and reticular dystrophy. One eye

of one patient developed solitary vitelliform pattern dystrophy during follow-up. Two patients showed progression from one pattern into another during follow-up. Another patient, who at first showed no evidence of pattern dystrophy in either eye, developed fundus pulverulentus in both eyes 5 years later. One patient had simultaneous evidence of 2 types: butterfly and fundus flavimaculatus pattern in each eye. Angioid streaks were seen in each eye of all patients. Peau d'orange was noted in 18 patients, optic nerve drusen in 5, and retinal crystalline bodies in 9. Choroidal neovascular membrane was present in 15 patients.

Conclusions: All 5 varieties of pattern dystrophy, 2 of which were not previously associated with PXE, were seen in patients with PXE. Fluorescein angiogram was useful in delineating the type and extent of pattern dystrophy.

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PSEUDOXANTHOMA ELASTICUM (PXE) is a hereditary systemic disease of the connective tissue affecting 1 in 100 000 Americans.¹ Pseudoxanthoma elasticum is characterized by progressive calcification, fragmentation, and degeneration of elastic fibers in the skin, eye, and cardiovascular system. The main external indicator of PXE is the "plucked chicken" appearance of the skin. These are small yellowish macules, papules, or plaques occurring most commonly on the back of the neck, the antecubital fossa, and other flexor surfaces.²⁻⁶ Other systemic manifestations of the disease include calcification of elastic media and intima of arteries and heart valves, resulting in renal artery stenosis, intermittent claudication, and mitral valve prolapse. Gastrointestinal hemorrhage, usually gastric in origin, is due to bleeding from fragile calcified submucosal vessels. Occasionally, bleeding can occur in the urinary tract or the cerebrovascular system.

Almost all patients with PXE develop ocular disease. The most common ocular findings are angioid streaks, which are

cracks in the Bruch membrane seen in 85% of patients with PXE. Because angioid streaks have also been associated with Paget disease and sickle cell disease,^{2,7} the presence of angioid streaks alone in the absence of other features of PXE and a negative family history cannot serve as evidence of PXE.⁵ Other ocular features associated with PXE include peau d'orange, optic nerve drusen, retinal crystalline bodies, focal atrophic pigment epithelial lesions, and pattern dystrophy of the macula.⁸⁻¹⁰

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Pattern dystrophy is an autosomal dominant condition described by Sjogren¹¹ for the first time in 1950. Pattern dystrophies have been subclassified into 5 groups based on the pattern of pigment distribution. These include vitelliform dystrophy of the fovea, fundus flavimaculatus, reticular dystrophy of the pigment epithelium, fundus pulverulentus, and butterfly-shaped pigment dystrophy of the fovea.^{8,12} To our knowledge, the incidence and association of all 5 subclasses of pattern dystrophy with PXE have not

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Table 1. Demographic Characteristics and Fundus Features in 22 Patients With PXE*

Patient No./Sex/ Age, y	Dx Confirmation	Final Visual Acuity	Length of Follow-up	Peau d'Orange	Disc Drusen	Crystalline Bodies	CNVM	Pattern Dystrophy	Type
1/M/57	Fundus findings	OD: 20/80 OS: 1/200	9.5 y	+	-	-	+	-	-
2/M/54	Fundus findings	OD: CF at 60 cm OS: 20/40 - 2	3 y	+	-	-	+	+	FP FP→VIT/BF
3/F/74	Fundus findings	OD: 20/200 OS: 20/40	1 d	+	-	-	-	+	FP
4/M/65	Fundus findings	OD: NA OS: NA	3 mo	+	-	-	+	+	FP FP
5/M/76	Clinical examination	OD: 20/25 OS: 20/60 - 2	29 y	+	-	-	+	-	-
6/F/65	Clinical examination	OD: CF at 25.4 cm OS: 20/200	14 mo	-	-	+	-	-	-
7/F/45	Clinical examination	OD: 20/60 OS: 20/100 - 2	11 mo	+	-	+	+	-	FP
8/F/74	Fundus findings	OD: 20/400 OS: 20/200	43 y	+	-	-	-	-	-
9/F/74	Clinical examination	OD: 20/70 - 1 OS: LP	1.5 y	+	-	-	-	+	FP FP
10/F/73	Skin biopsy specimen	OD: 20/200 OS: 20/300	19.5 y	-	-	-	-	+	FP FP
11/F/65	Fundus findings	OD: 20/400 OS: 8/200	7 y	-	-	+	+	+	FP FP
12/F/48	Clinical examination	OD: 20/200 - 1 OS: 20/200	9 y	+	-	+	-	+	FP→R FP→R
13/F/43	Fundus findings	OD: 20/25 - 3 OS: 20/20 - 3	1 d	+	-	+	-	-	-
14/M/57	Clinical examination	OD: 20/200 OS: 20/20	5 y	+	+	-	+	+	None→FP None→FP
15/F/51	Fundus findings	OD: 20/30 OS: 20/40	1 d	+	+	+	+	+	BF/FF BF/FF
16/M/41	Fundus findings	OD: 20/200 OS: 20/200	10 mo	+	-	-	-	+	FP FP
17/F/65	Fundus findings	OD: 20/25 OS: 20/40	2 y	+	-	-	+	+	FP FP
18/F/41	Clinical examination	OD: 20/20 OS: CF	1 d	+	+	+	-	-	-
19/F/46	Fundus findings	OD: 2/200 OS: NA	3 mo	+	-	+	+	+	FP
20/M/46	Clinical examination	OD: 20/100 - 2 OS: 3/200	1 wk	-	-	-	+	+	FP
21/F/45	Fundus findings	OD: 20/200 OS: 20/200	3.5 y	+	-	-	-	-	-
22/M/68	Fundus findings	OD: 20/20- OS: 20/40-	6 mo	-	-	-	-	+	BF BF

Abbreviations: BF, butterfly; CF, counting fingers; CNVM, choroidal neovascular membrane; Dx, diagnosis; FF, fundus flavimaculatus; FP, fundus pulverulentus; LP, light perception; NA, data not available; PXE, pseudoxanthoma elasticum; R, reticular; VIT, vitelliform; +, present; -, absent.
*Angioid streaks were found in both eyes of all patients.

been reported. McDonald et al³ described a spectrum of peculiar reticularlike pattern in the fundus in 9 patients with PXE. The present study describes the more complete spectrum of pattern dystrophy with PXE.

METHODS

To further explore the association between the 5 subclasses of pattern dystrophy and PXE, a cross-sectional study was conducted at the Vanderbilt Eye Institute. No known predisposition to PXE exists in the population patronizing this clinical practice.

The criteria for inclusion in the study consisted of a positive diagnosis for PXE and availability of the patient's medical

and photographic records. The 23 patients consisted of 8 men ranging in age from 41 to 76 years and 15 women ranging in age from 41 to 74 years.

To confirm a positive diagnosis for PXE, the Vanderbilt University Medical Center medical records for each of the 23 patients were carefully reviewed. Based on the information obtained from the records, each patient's PXE diagnosis was labeled as being confirmed by a skin biopsy specimen, a clinical examination, or fundus findings (constellation of angioid streaks, peau d'orange, and choroidal neovascular membrane). Color fundus photographs of all 46 eyes and fluorescein angiograms (when available) were reviewed. The presence of ocular findings characteristic of PXE, such as angioid streaks, peau d'orange, optic nerve drusen, crystalline bodies, choroidal neovascular

membrane, and pattern dystrophy, was noted. The fundus appearance of pattern dystrophy was categorized into the 5 types, as previously described. Some patients with follow-up photographs were also studied for progression of ocular disease. All of the data obtained from the review of the medical records and the photographs were compiled in a database.

RESULTS

Of the 23 subjects meeting the patient selection criteria, 22 had a positive diagnosis for PXE after review of the medical history information. The diagnosis was confirmed by fundus findings in all 22 patients, by a clinical examination of the skin in 9, and by a skin biopsy specimen in 1.

Pattern dystrophy was present in 16 patients (27 eyes) of those with PXE. Of the patients, 14 (23 eyes) had fundus pulverulentus, 3 (5 eyes) had butterfly-shaped dystrophy, and 1 (2 eyes) each had fundus flavimaculatus and reticular dystrophy. One eye of one patient developed the solitary vitelliform pattern during follow-up (**Table 1**). Patient 2 had fundus pulverulentus in both eyes, which progressed into the butterfly and vitelliform patterns in the left eye. Patient 15 had the butterfly pattern and fundus flavimaculatus in each eye.

Two patients showed progression from one pattern into another during follow-up. In one patient (patient 12) who initially was seen with fundus pulverulentus in both eyes

(**Figure 1**), the pattern progressed into the reticular type 9 years later in both eyes (**Figure 2A-D**). In patient 2, with preexisting fundus pulverulentus dystrophy (**Figure 3**), there was a change into the butterfly type and the appearance of yellow vitelliform material in the subretinal space in his left eye 2 years after he was initially seen (**Figure 4A-C**).

Another patient (patient 14) who at first showed no evidence of pattern dystrophy in either eye developed fundus pulverulentus in both eyes 5 years later (**Figure 5A and B**).

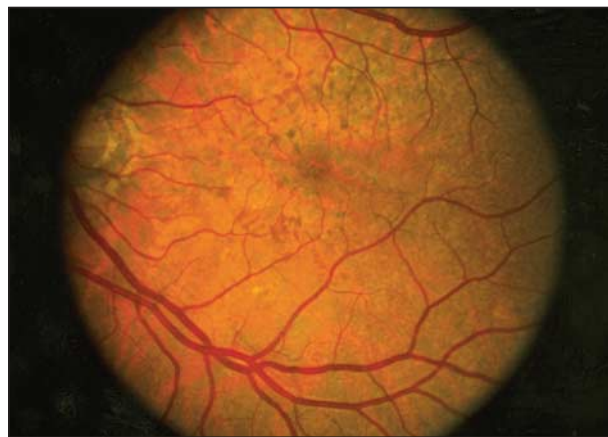


Figure 1. Left macula of patient 12, with features of fundus pulverulentus.

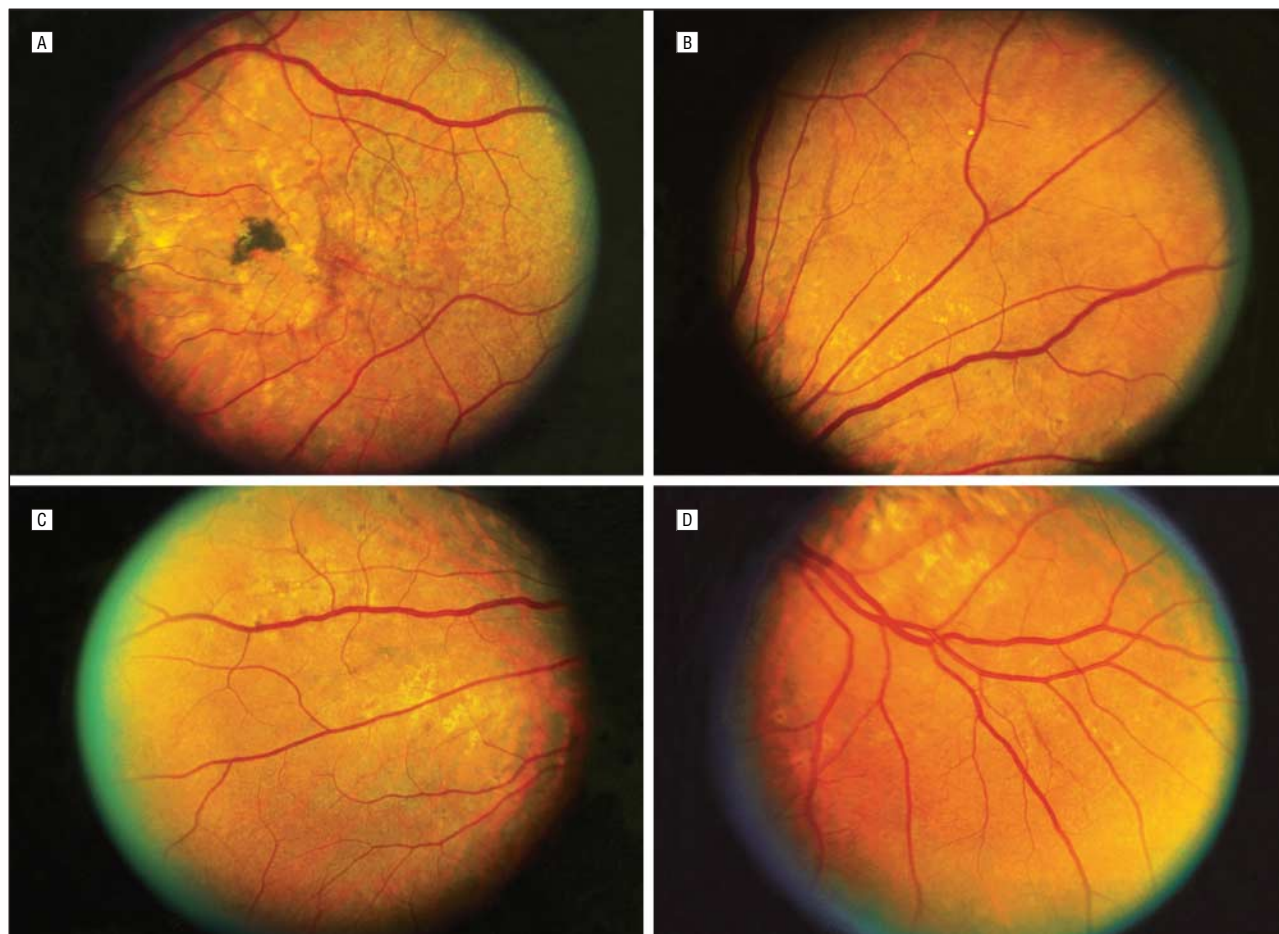


Figure 2. Patient 12 showing extensive progression into the reticular type of pattern dystrophy 9 years later (A-D).

One patient (patient 15) had simultaneous evidence of 2 types: butterfly and fundus flavimaculatus in each eye (**Figure 6A** and **B**). The macula showed radiating pigment lines of the butterfly pattern, and the area near the superior temporal vessels showed yellow triangular flecks resembling fundus flavimaculatus. Because of inadequate follow-up information, we were unable to monitor progression from one pattern to another in other patients.

Angioid streaks were seen in each eye of all patients. Peau d'orange was noted in 18 patients, optic nerve dru-

sen in 5, and crystalline bodies in 9. Choroidal neovascular membrane was present in 15 patients (**Table 2**).

COMMENT

The earliest description of possible association of pattern dystrophy with PXE dates to the report of mottled fundus in the fellow eye of a patient with angioid streaks by Pagenstecher¹³ in 1941. Zeeman¹⁴ in 1933, Bischler¹⁵ in 1955, and Shimizu¹⁶ in 1961 have all described patients with fundus mottling. To our knowledge, the report by Smith et al¹⁷ in 1964 is the first description of pattern dystrophy in association with angioid streaks in the United States. Gills and Paton¹⁸ described 2 siblings and a mother with mottled fundus in addition to other features of PXE. Erkkila et al⁴ described a PXE patient with a firework pattern of pigment dispersion in both macula.

McDonald et al,^{3(pp306,310)} in a series of 14 consecutive patients, found 9 patients (18 eyes) who had peculiar pigmentary changes in the retina. Ten eyes had a "random pigment dot pattern," 4 eyes showed a linear arrangement of pigment dots resembling "string of pearls," and 4 others had pigment clumping that occurred in a "fish-net or reticular pattern." Studying their photographs, the random dot pattern corresponds to the fundus pulverulentus type of pattern dystrophy. When these pigment

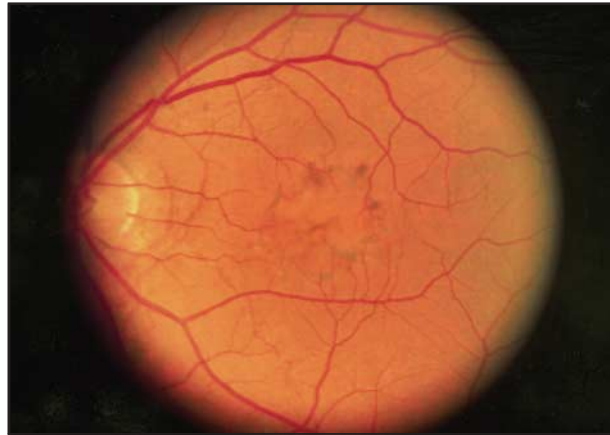


Figure 3. Patient 2 had fundus pulverulentus when first seen.

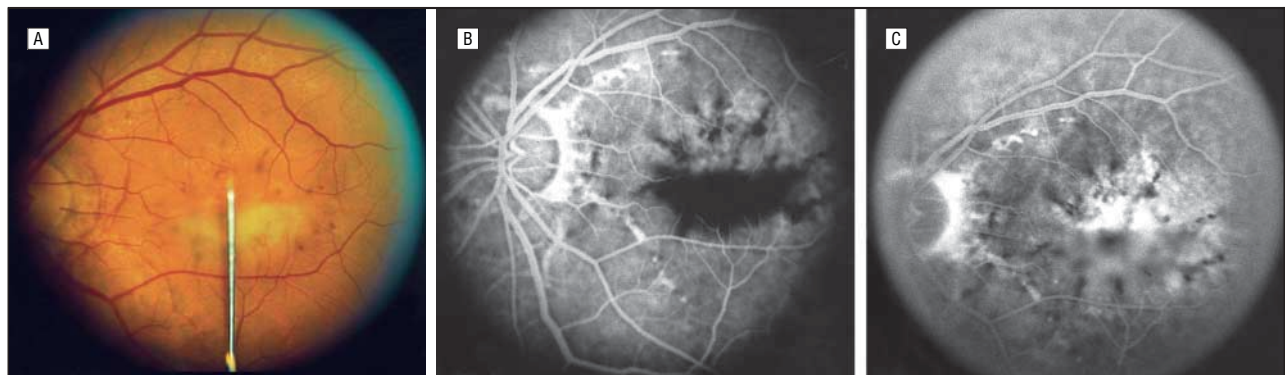


Figure 4. Patient 2 showing progression from fundus pulverulentus into butterfly and vitelliform dystrophy 2 years later (A), an early fluorescein angiogram depicting the butterfly pattern and showing blocked fluorescence from the yellow material (B), and a late fluorescein angiogram showing partial staining of the yellow material (C).

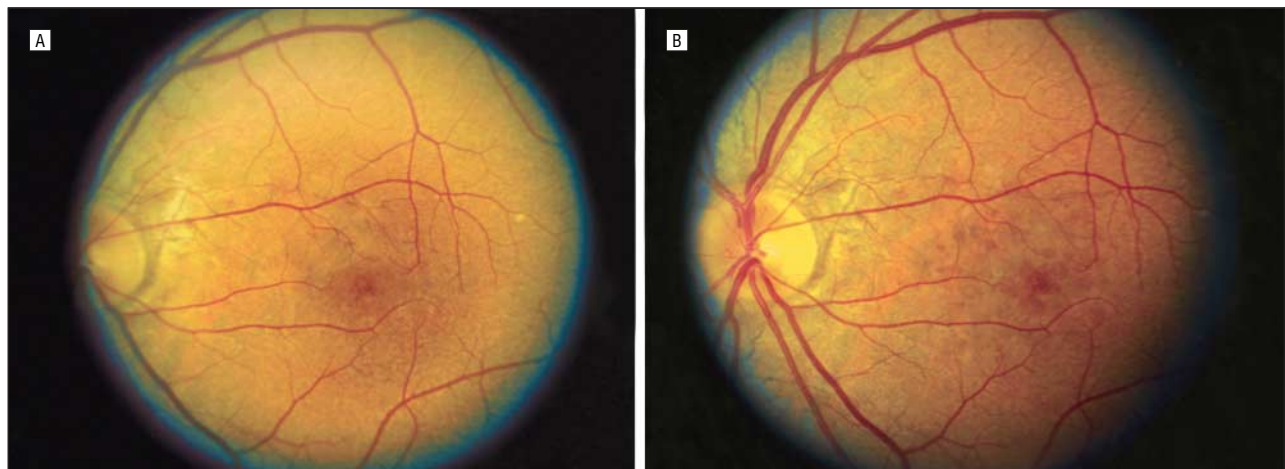


Figure 5. Patient 14 had no evidence of pattern dystrophy initially (A) and had fundus pulverulentus 5 years later (B).

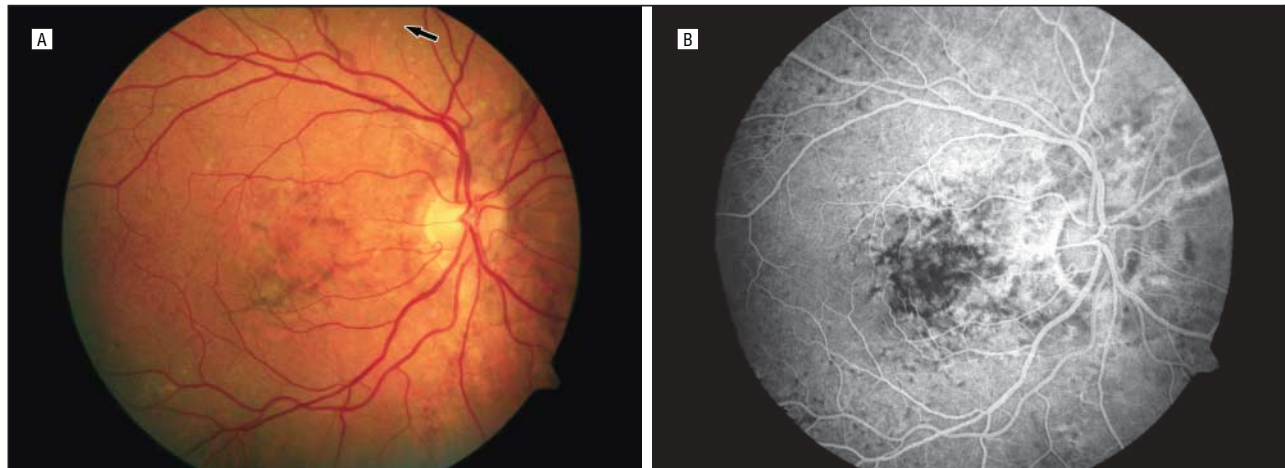


Figure 6. A butterfly pattern in the fovea and fundus flavimaculatus type (arrow) of pattern dystrophy near the arcades in the same eye of patient 15 (A) and a fluorescein angiogram without a “dark choroid” differentiates the condition from typical fundus flavimaculatus (B).

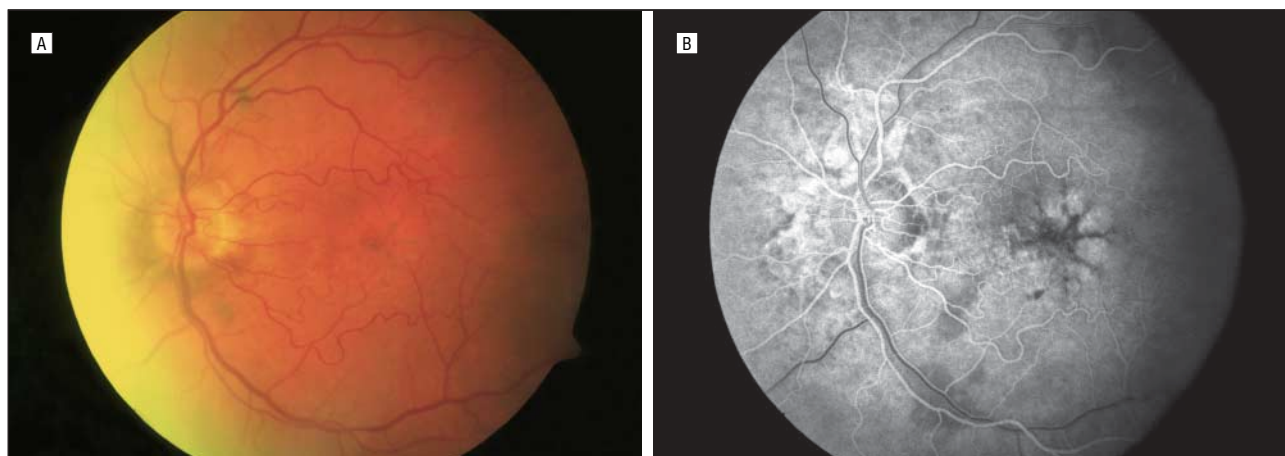


Figure 7. The presence of pattern dystrophy in patient 22 was more evident on the fluorescein angiogram than on the color picture (A and B).

dots are connected in a stringlike fashion or more extensively to resemble a fishnet, the condition is described as the reticular type.

In this series, we attempted to look for the presence of further types of pattern dystrophy in patients with PXE. Of the 22 patients, 16 (27 eyes) showed evidence of pattern dystrophy. The most common type seen was fundus pulverulentus in 13 patients. The fundus in these patients showed coarse punctate mottling of the pigment epithelium in the central macular region. The pigment change in some patients was more evident on the fluorescein angiogram than on the clinical examination, an observation that has been made previously³ (**Figure 7A** and B).

Butterfly pattern dystrophy was seen in 5 eyes of 3 patients. The pigment granules were distributed symmetrically, disrupting the normal orange color of the macula to resemble a butterfly. Patient 15, in addition, showed pisciform yellow lesions at the level of the retinal pigment epithelium, resembling the flecks of fundus flavimaculatus. Patients with dominantly inherited pattern dystrophy without PXE may show different patterns in the 2 eyes. Combinations of any of the 5 subclassifications may also occur in a single eye.¹² Examination of the various members of a pedigree may show different patterns in each of the affected members. To our knowl-

Table 2. Associated Fundus Findings in Patients With PXE

Finding	No. (%) of Eyes	No. (%) of Patients
Angioid streaks	44 (100)	22 (100)
Peau d'orange	30 (68)	18 (82)
Optic nerve drusen	8 (18)	5 (23)
Retinal crystalline bodies	13 (30)	9 (41)
CNVM	19 (43)	15 (68)
Pattern dystrophy	27 (61)	16 (73)

Abbreviations: See Table 1.

edge, the finding of the butterfly and fundus flavimaculatus type of pattern dystrophy in patients with PXE has not been previously reported.

Vitelliform dystrophy of the fovea is characterized by the appearance of egg yolk–like subretinal lesions and the possible presence of small yellow flecks.^{8,13} This was seen in patient 2, who also showed the butterfly type of dystrophy beneath the yellow change in both eyes.

Patients with reticular dystrophy exhibit a highly organized network of pigment flecks resembling a fishnet or chicken wire.^{8,13,15} In the series by McDonald et

al,^{3(pp306,309,310)} the patients were described as having a “spectrum of reticular-like pigment patterns.” Ten of these eyes had random scattering of pigment dots that fit in with the description of fundus pulverulentus. Four eyes had a string-of-pearl-like distribution of pigment, and 4 others had a truly reticular pattern with a fishnetlike appearance. It is conceivable the string-of-pearl pattern may be a forme fruste of reticular dystrophy. Only one patient (patient 12 [2 eyes]) in our series showed a reticular pattern.

Patient 14, who initially had no evidence of pattern dystrophy, developed fundus pulverulentus during follow-up, 5 years after he was initially seen. This feature of appearance of pattern dystrophy on follow-up has been well documented in an autosomal dominant pattern dystrophy without associated systemic disease.⁹

Pattern dystrophy has also been described in association with myotonic dystrophy, Kjellin syndrome, and in one patient with McArdle disease (muscle phosphorylase deficiency).¹⁹⁻²² Burian and Burns¹⁹ described coarse clumps of pigment, some of them radiating from the fovea in a streaklike pattern in patients with myotonic dystrophy. When the streaks were multiple, they seemed to have a stellate appearance. Studying the photographs in their article, the pattern seems to fit into fundus pulverulentus and the reticular type of pattern dystrophy. The fundus appearance of one patient with McArdle disease is typical of reticular pattern dystrophy.²² Kjellin syndrome is an autosomal recessive disorder characterized by spastic paraplegia, dementia, and retinal flecks.²¹ The flecks in this disorder resemble the fundus flavimaculatus type of pattern dystrophy.

Most of our patients with PXE showed several of the ocular findings associated with PXE. Angioid streaks were observed in 100% of our patients, because only patients with streaks were in our photography database. Other fundus findings included peau d'orange, optic disc drusen, retinal crystalline bodies, and choroidal neovascular membrane. Because not all patients had photographs beyond the posterior pole, the incidence of peau d'orange and retinal crystalline bodies may be underestimated.

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